Paediatric pulmonary hypertension

Loon, Rosa Laura Elisabeth van

CHAPTER

Summary
Nederlandse samenvatting
Sinopsis en español

SUMMARY

Pulmonary hypertension (PH), defined by a mean pulmonary arterial pressure of ≥25 mmHg, is a hemodynamic condition which can occur in the setting of various underlying conditions, as summarized by the clinical classification of PH (Table 1, Chapter 1). One of these conditions is pulmonary arterial hypertension (PAH), which is a rare progressive and life-threatening pulmonary vascular disease. PAH can occur idiopathically (iPAH) or associated with underlying conditions such as congenital heart defects (PAH-CHD). One group of PAH-CHD is represented by the Eisenmenger syndrome. During the past decades there has been increased understanding of the pathobiology of PAH in particular, leading to the development of several second generation PAH drugs (prostanoids, endothelin receptor antagonists, 5-phosphodiesterase inhibitors). At the same time, the clinical classification of PH has undergone several modifications in order to categorize the various underlying conditions for PH and PAH in a pathophysiologically and clinically coherent manner. The general acceptance of this clinical classification has allowed improvements in standardization of diagnosis and treatment of PAH.

PH and PAH can occur at both the adult and paediatric age. However, most clinical and all epidemiological data on PAH has been derived from studies in adults. These results cannot be simply extrapolated to children with the disease, since children with PH and PAH have been reported to present with age group specific disease entities and clinical course. Paediatric PAH is rare and therefore, data is limited. The main aim of this thesis was to extend the available data on children with PH, regarding epidemiological features, clinical course and effects of new therapies. With this data insight into the disease in children can be gained and recommendations for improvements in disease management can be given.

In **Chapter 2** we reviewed PAH-CHD, one of the most common forms of PAH among children. This chapter discusses the heterogeneous character of this group of PAH in children. PAH-CHD is unique from other subgroups of PAH, in that a reversible stage of the disease can be discerned. Thus, PAH-CHD represents a spectrum with the Eisenmenger syndrome (and irreversible pulmonary vascular disease) at the severe end and, at the other end, young paediatric patients in whom repair of the CHD leads to prevention or regression of the early stage of PAH (flow-PAH, as illustrated in Chapter 3). The wide variety of CHD and their different circulatory physiology also make PAH-CHD a heterogeneous disease. Furthermore, the clinical course of PAH-CHD among children may be complicated by accelerated forms of PAH-CHD as well as the presence of multiple other conditions associated with PAH, such as obstructive breathing disorders and/or genetic anomalies. The clinical presentation and disease course of these groups of children are illustrated further in Chapters 3 and 4. Regarding supportive treatment and the effects of PAH drugs, PAH-CHD demands specific considerations, which are summarized in this chapter and illustrated further in Chapters 5, 7 and 8.

Chapter 3 describes nationwide data on the epidemiological features of paediatric PH in the Netherlands encompassing a 15-year period. This study illustrates that paediatric

PH is characterized by age group specific disease entities. The great majority of these comprised transient forms of PAH (>80%), represented by persistent pulmonary hypertension of the neonate (PPHN, 47%) and flow-PAH (34%). Other paediatric age-group specific diagnoses included PH associated with chronic lung disease of prematurity (2%) and congenital diaphragmatic hernia (4%). Progressive PAH accounted for 5% of all patients, with iPAH (23%) and PAH-CHD (72%) representing the most common subgroups. PAH-CHD constituted a heterogeneous group of diagnoses, including Eisenmenger syndrome, accelerated forms of PAH-CHD and PAH-CHD persisting or developing after closure of the shunt defect. Syndromes and syndromal abnormalities were common, especially in patients with progressive PAH (39%).

Annual incidence rates for all PH diagnoses averaged 63.8 cases per million children. For PAH-CHD and iPAH, annual incidence rates and point prevalence averaged, respectively, 2.2 and 15.6 (PAH-CHD) and 0.7 and 4.4 (iPAH) cases per million children. The incidence rates for PAH-CHD declined over the years. Compared to adults, incidence and prevalence rates for paediatric PAH-CHD were higher. In contrast, these rates for paediatric iPAH were lower. Survival for all PAH-CHD subgroups together was better than for iPAH. However, specific subgroups showed worse or similar survival compared with iPAH. Survival of children with Eisenmenger syndrome appeared to be worse than in adults with the disease.

Chapter 4 describes the clinical presentation of a cohort of paediatric patients with suspected PAH, seen within the Dutch "Network for Diagnosis and Treatment of Paediatric PAH". This chapter focuses on the extensive diagnostic process needed for adequately determining the explanatory role of associated conditions for the PAH and for determining the subgroup diagnosis of PH. In this study, almost 75% of children with suspected PAH had one or more underlying conditions. However, these associated conditions, which included CHD, obstructive breathing disorders and connective tissue disease were not always explanatory for the PAH. In 25% of the children in whom an associated condition was identified, this condition was not primarily explanatory for the PAH. Forty-three % of the CHD and 53% of obstructive breathing disorders were not explanatory for the P(A)H. Ultimately, about half of the children were classified as iPAH and the other half as PAH-CHD. Interestingly, genetic syndromal abnormalities co-occurred in 43% of all patients, a similar number as observed in Chapter 3.

The patients with PAH described in Chapter 4 are studied further regarding their outcome and the effects of PAH drugs on their outcome in **Chapter 5**. This chapter describes that with the introduction of second generation drugs the overall survival of these children with PAH improved compared to calculated historical survival. In order to analyze the survival further, we divided the patients into 3 study groups based on their time of diagnosis in relation to the availability of second generation drugs. The improved survival appeared to be mainly driven by patients for whom second generation drugs were not available at time of diagnosis, but became available during their disease course. In contrast, patients for whom second generation drugs were already available at time of diagnosis did not show improved survival. Initiation of second generation drugs

induced clinical and laboratory improvements during short-term follow-up, but these improvements declined in the longer term, a similar finding as in Chapter 7. Both invasive hemodynamic assessments as non-invasive assessments (World Health Organisation functional class, 6-minute walk distance and the serum markers NT-proBNP and uric acid) were predictors for survival. The results of this study suggest that in paediatric PAH more aggressive treatment strategies, resulting in more frequent and earlier use of combination therapy, should be considered.

In the determination of the prognosis and appropriate treatment course of patients with PAH, acute pulmonary vascular response to vasodilator challenge plays a central role. However, there has been discussion on how to define this response and on its applicability in different PAH patient groups. **Chapter 6** highlights that the prevalence of acute pulmonary vascular response to vasodilator challenge differs depending on the used criteria. Importantly, in contrast to what was generally acknowledged, this study could not demonstrate a higher prevalence of response in children than in adults. Furthermore, this study demonstrates that the currently used criteria (based on a decline in mean pulmonary arterial pressure) are not applicable to patients with PAH-CHD and unrestrictive post-tricuspid shunt. Instead, criteria based on the ratio between pulmonary and systemic vascular resistance and the ratio between pulmonary and systemic blood flow may be more suitable for the identification of responders in this group of patients.

In **Chapters 7 and 8** studies are described which specifically evaluate the treatment effects of the dual endothelin receptor blocker bosentan, in children and adults with PAH-CHD. Both studies describe improvements in 6-minute walk distance and functional class during short-term follow-up. However, on the long-term these improvements gradually returned to baseline value. This long-term attenuation appeared to be more profound in the children. Furthermore, survival for the children was worse than for the adults with PAH-CHD. In Chapter 8, half of the adult patient group had Down's syndrome. In these patients, 6-minute walk distance could not be performed fully adequately. Therefore, its use in this patient group is questionable and the value of additional, non-invasive assessments needs to be evaluated further in these patient groups.

Despite the improvements in outcome with second generation PAH drugs, PAH remains a progressive and incurable disease. Therefore, further unravelling and understanding of the pathobiology of the disease is necessary in order to develop new medications and improve treatment. In **Chapter 9** we studied the effects and possible downstream mechanisms of erythropoietin (EPO) treatment in an experimental rat model of flow-associated PAH. EPO treatment has been observed to improve pulmonary vascular remodelling in PAH. In order to test the hypothesis that EPO improves this pulmonary vascular remodelling through induction of heme oxygenase (HO) activity and mobilization of endothelial progenitor cells (EPCs), we treated rats with flow-associated PAH with EPO with and without a potent HO-activity inhibitor, tin mesoporphyrin (SnMP). HO is an enzyme which protects against oxidative stress and inflammation through the production of its reaction products (ferrous iron, carbon monoxide and biliverdin). This study showed that the improvements in pulmonary vascular remodelling by EPO were not

mediated by increased activation of HO, but were accompanied by increased numbers of circulating EPCs. Interestingly, inhibition of HO-activity by SnMP, alone or in combination with EPO treatment, also resulted in increased numbers of circulating EPCs. However, despite increasing the number of circulating EPCs, inhibition of HO-activity worsened the pulmonary vascular remodelling. This indicates that both EPO and HO have beneficial effects on PAH. Furthermore, our data suggests that HO may be required for EPCs to home to the diseased pulmonary vascular bed.

In **Chapter 10** the main findings of this thesis are discussed in a broader perspective with a particular focus on possible future studies.